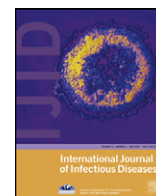


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A study of adherence to antibiotic treatment in ambulatory respiratory infections

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SUMMARY

Objectives: To assess the different types of antibiotic-taking behavior and to compare self-reported with objectively measured adherence to antibiotic regimens in respiratory infections.**Methods:** This was a prospective study of patients with suspected bacterial pharyngitis and lower respiratory tract infections recruited from five primary care clinics in Catalonia. Adherence to various antibiotic regimens was assessed by the Medication Event Monitoring System (MEMS), which recorded every opening of the patient's bottle of tablets, and a self-reported adherence question. The outcome variables were antibiotic-taking adherence, correct dosing, and timing adherence.**Results:** A total of 428 patients were included in the analysis. Five types of antibiotic use behavior were observed: excellent adherence (130 patients, 30.4%), acceptable adherence over time (53; 12.4%), declining adherence over time (123; 28.7%), non-adherence to correct dosing (108; 25.2%), and unacceptable adherence (14; 3.3%). Excellent adherence was significantly associated with the number of daily doses of antibiotic and antibiotic duration. A total of 254 patients reported never forgetting to take the antibiotic (59.3%), achieving a negative predictive value of 100% and a positive predictive value of 51.2%.**Conclusions:** Outpatients with respiratory infections treated with antibiotics showed poor adherence outcomes. Self-reported adherence was remarkably higher than that observed with the use of MEMS and failed to predict true patient adherence.

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1. Introduction

Medical adherence is defined as the extent to which a patient's taking of medication is consistent with medical or health advice.¹ Non-adherence to medications is particularly important in clinical practice. Adherence to medications has long been a concern because it often affects the outcome of treatment. In a review of 63 studies over a 30-year period, the authors reported that if the patient is adherent, the odds of a good outcome are almost three-fold higher than for those who are non-adherent.² In the case of infectious diseases, non-adherence to antibiotics might also lead to the storing of antibiotics at home, which induces self-medication, leading to a vicious circle, and thereby favoring the emergence of bacterial resistance.³

Measuring adherence is difficult because most of the direct and indirect measures available have limitations. Since their introduction in 1986, microelectronic devices have become the gold

standard in adherence research.⁴ The most commonly used system is the Medication Event Monitoring System (MEMS). MEMS medication bottles contain a microelectronic chip that registers the date and time of opening of every bottle. Assuming that the opening of a bottle represents the intake of medication, MEMS provides a detailed profile of the patient's adherence behavior. For this reason, MEMS is currently regarded as the gold standard for the measurement of adherence.^{5–7} MEMS have been used to monitor adherence mainly with long-term medications, and in the case of infectious diseases, this technology has particularly been used to track medication adherence with antiretroviral agents and with anti-tuberculosis drugs. However, data on the antibiotic-taking behavior in respiratory tract infections in the community are lacking.⁷ With the use of MEMS we previously observed that adherence to antibiotic regimens in respiratory infections decreased with an increase in the number of daily doses.⁸

Simple questions are the most commonly used measures of treatment adherence in medical consultation. The simplest question is asking if the patient has taken the treatment as requested. Physicians assume that patients provide honest answers and we usually believe their responses. However,

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self-reported questions may often provide inflated estimates of adherence behavior.⁹ The use of a non-judgmental, non-threatening approach is therefore recommended, preceding the question with a remark such as the following: “People often have difficulty taking their pills for one reason or another”, before asking if the patient has missed any dose.¹⁰ The use of this approach decreases the overestimation of true adherence in chronic disorders, but the benefit of this in acute conditions such as respiratory tracts infections remains unanswered. In the current study we aimed to assess the different types of antibiotic use behavior among patients with respiratory tract infections and to compare the performance of a self-reported adherence question with objectively measured adherence of antibiotic regimens in these infections.

2. Methods

We performed a prospective, observational study in five general medicine outpatient clinics from 2003 to 2008 in Catalonia, Spain. We recruited patients aged 18 years or older presenting to the primary care practice with uncomplicated, acute (<7 days), suspected bacterial pharyngitis and lower respiratory tract infections. We excluded patients who had received previous treatment with antibiotics, those who presented criteria for hospitalization, those with any condition requiring the aid of other persons for drug administration, and those with hypersensitivity to antibiotics. The patients were treated with different antibiotic regimens previously included in the MEMS (Aardex Group Ltd, Zug, Switzerland) containers. The physicians decided which of these antibiotic treatments was to be administered.

Before the initiation of the study, the Spanish health authorities were informed about its characteristics and how it was to be conducted. Spanish legislation at the time of the study determined that institutional review board approval was not required for observational studies. However, the patients gave informed consent to participate in a study on the rational use of antibiotics. They were provided with complete information about the characteristics of the study and their participation, but were not informed at that time about the future assessment of adherence to avoid bias in the results. When they returned to the clinic, the physician collected the MEMS container and self-reported adherence was evaluated by means of the following question: “We almost always forget to take all of the pills, did you ever forget to take any?” Patients were fully informed about the results, and permission was requested to include these data anonymously in the current report. All the data included in the database were encoded to ensure confidentiality. The data contained in the microprocessors were transferred to the computer and processed with PowerView program v. 1.3.2. (Aardex Ltd). Multiple openings of the container within a period of less than 15 min were not counted.

2.1. Adherence parameters

Three different outcome measures were taken into account: (1) ‘Taking adherence’, calculated as the percentage of times the container was opened during the course of the treatment, related to the total number of pills included in the container. Good taking adherence was considered when it was greater than 80%. (2) ‘Correct dosing’, calculated as the number of days on which the patient opened the container at least the prescribed number of times, that is, at least three times for those assigned to the three times-daily antibiotics, twice for patients treated with twice-daily regimens, and once for those receiving once-daily antibiotic courses. For twice- and three times-daily regimens, dosing on day 1

may be restricted due to the late start of treatment (after visiting the physician), and this has to be taken into account. Good correct dosing was considered when it was greater than 80%. (3) ‘Timing adherence’, indicating whether the opening of the container coincided with the times recommended: intervals of 8+4 h during at least 80% of the three times-daily courses of antibiotics, 12+6 h intervals during at least 80% of the antibiotic course for the twice-daily antibiotics, and 24+12 h intervals during at least 80% of the antibiotic course for the once-daily antibiotics.

Excellent adherence was defined when these three adherence outcomes were good.

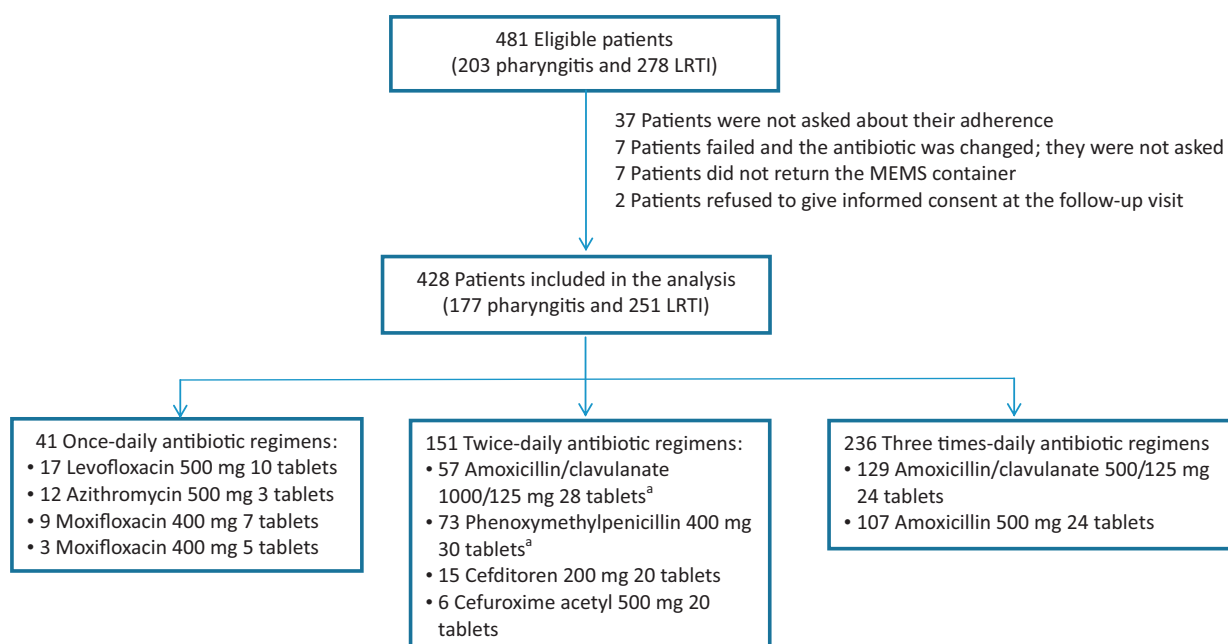
2.2. Statistical analysis

Descriptive statistics were used to describe the different adherence parameters observed in this study. We used Chi-square tests to compare proportions. The sensitivity, specificity, and positive and negative predictive values of the self-reported adherence question were determined with a two-way contingency table, using the adherence parameters provided by MEMS as the gold standard. A logistic regression model was constructed to identify variables significantly and independently associated with excellent adherence. The variables were included in the model if they were associated with a high score with a *p*-value of <0.10. Variables were eliminated from the model using the stepwise automatic variable screening method, the alpha thresholds for inclusion and exclusion being set at 0.20. Statistical significance was accepted at *p* < 0.05.

3. Results

A total of 481 patients were recruited. The self-reported adherence question was not registered for 37 patients. Furthermore, seven antibiotic treatment failures were observed requiring a change in antimicrobial treatment, and the adherence question was not evaluated in these cases. Seven patients did not return the MEMS container and two more refused to give consent (Figure 1). Of the 428 patients with complete information available for analysis, 236 (55.1%) received antibiotics three times daily, 151 received twice-daily antibiotic regimens, and the remaining 41 patients received once-daily antibiotic schedules. The different antibiotics used are described in Figure 1. A total of 251 patients (58.6%) were diagnosed with a lower respiratory tract infection and the remaining 177 patients were diagnosed with suspected bacterial pharyngitis. The mean age of all the patients was of 47.1 ± 21.2 years, and 231 were females (54.0%).

A total of 265 patients opened the vial at least 80% of the times (61.9%), 146 presented correct dosing adherence (34.1%), and 165 achieved good timing adherence for at least 80% of the antibiotic course (38.6%). Five patterns of antibiotic taking behavior were observed in this study: 130 patients (30.4%) achieved 80% of all the adherence outcomes and therefore presented excellent adherence. Another 53 patients (12.4%) missed only one dose for achieving excellent adherence and presented a relatively acceptable adherence during the antibiotic course. A total of 123 patients (28.7%) presented declining adherence over time with good correct dosing at the beginning of the antibiotic course followed by a reduction in the daily doses along the remainder of the course until the end. Thirteen of these patients (10.6%) abruptly stopped taking the tablets in the first half of the medication course. A total of 108 patients (25.2%) presented non-adherence to consistent correct dosing over time and 14 (3.3%) presented an unacceptable adherence pattern, with incorrect dosing and a further decline. The adherence parameters were consistently worse with three times-daily antibiotic regimens and better with once-daily courses (*p* < 0.001) (Table 1).



^aPatients were recommended to take two tablets every 12 hours

Figure 1. Flow of patients through the study.

Candidate variables included in the multivariate regression analysis were the patient characteristics (age, gender, presence of high blood pressure, dyslipidemia, or diabetes mellitus, smoking status, and retired or not) and antibiotic-related variables (daily doses, duration, and presence of adverse effects). Excellent adherence was significantly associated with the number of daily doses of the antibiotic (odds ratio (OR) 0.22, 95% confidence interval (CI) 0.15–0.32) and antibiotic duration (OR 0.77, 95% CI 0.61–0.96).

A total of 254 patients answered the self-reported adherence question (good self-reported adherence) negatively (59.3%). The remaining patients answered either affirmatively or elicited an unclear response. A total of 304 patients were correctly identified by this approach (71.0%). All patients presenting excellent adherence by means of the MEMS determination reported never forgetting to take their medications. On the other hand, the answer was negative in only 124 of the 298 patients who did not present excellent adherence (41.6%). As shown in Table 2, the negative predictive value of the question was 100%, with a positive predictive value of 51.2%. Table 3 describes the different responses depending on the type of antibiotic used.

4. Discussion

This study compared self-reporting with objectively measured medication adherence using an evidence-based cut-off point in the same study population. The main result of this study is that medication adherence objectively measured by MEMS was very

poor since only 30% of the patients presented excellent adherence. Furthermore, the use of self-reported adherence remarkably overestimated the true adherence.

Five adherence types were identified in this study by means of the MEMS method: excellent adherence, relatively consistent adherence over time defined as those patients who missed only one dose for achieving excellent adherence, declining adherence over time, non-adherence to correct dosing, and unacceptable adherence. In a qualitative semi-structured interview study of 46 people, Hawkins et al.¹¹ reported six different types of antibiotic user behavior: those who always took antibiotics as prescribed, could not take doses because of work, child care, or social constraints, frequently forgot doses, believed it made sense to stop taking antibiotics as they started to get better, actively sought to limit antibiotic use because they believed their own bodies became used to them or because antibiotics are unnatural, and deliberately planned to stop early so as to have an antibiotic supply for self-use in the future to avoid the challenges of consulting and obtaining antibiotics in primary care. In the Hawkins study, over a third of the respondents reported that they always took antibiotics as directed by the clinician or pharmacist. The results of the present study clearly indicate that less than a third of the patients took the tablets as requested. We used the same cut-off point recommended by the previous authors, i.e., at least 80% of all the adherence parameters evaluated.¹² However, only a little more than 12% of the patients nearly achieved these goals since they only missed one dose, and in all these cases the patients stated that they were adherent by

Table 1
Types of antibiotic-taking behavior depending on the number of daily doses in the antibiotic regimen

	Once-daily antibiotic regimen	Twice-daily antibiotic regimen	Three times-daily antibiotic regimen	Total
Excellent adherence	34 (82.9)	77 (51.0)	19 (8.1)	130 (30.4)
Acceptable adherence over time	5 (12.2)	23 (15.2)	25 (10.6)	53 (12.4)
Declining adherence over time	2 (4.9)	34 (22.5)	87 (36.8)	123 (28.7)
Non-adherence to consistent correct dosing	0 (0)	16 (10.6)	92 (39.0)	108 (25.2)
Unacceptable adherence	0 (0)	1 (0.7)	13 (5.5)	14 (3.3)
Total	41	151	236	428

Table 2

Validity of the self-reported adherence question

Response to the self-reported adherence question ^a	True adherence		Total
	Excellent	Not excellent	
Negative response (good self-reported adherence)	130	124	254
Affirmative or unclear response (not good self-reported adherence)	0	174	174
Total	130	298	428

^a We almost always forget to take all of the pills, did you ever forget to take any?

Sensitivity: 130/130 = 100%; specificity: 174/298 = 58.4%; positive predictive value: 130/254 = 51.2%; negative predictive value: 174/174 = 100%.

Table 3

Response to the self-reported adherence question depending on the antibiotic-taking behavior

Antibiotic-taking behavior	Response to the self-reported adherence question ^a		Total
	Negative response	Affirmative or unclear response	
Excellent adherence	130 (100)	0 (0)	130
Acceptable adherence over time	53 (100)	0 (0)	53
Declining adherence over time	47 (38.2)	76 (61.8)	123
Non-adherence to consistently correct dosing	23 (19.8)	85 (78.7)	108
Unacceptable adherence	1 (7.1)	13 (92.9)	14
Total	254 (59.3)	174 (40.7)	428

^a We almost always forget to take all the pills, did you ever forget to take any?

means of the self-reported adherence question. This demonstrates that the rationale for choosing a cut-off of 80% to define adherence in order to differentiate between adherence and non-adherence is arbitrarily chosen, and despite commonly being used by health professionals, it is not shared by patients who have to take the medication.

In our study, more than half of the patients with non-adherence to consistently correct dosing and declining adherence over time admitted to have forgotten some doses. Incorrect dosing is more linked to unintentional non-adherence, since it is influenced by the constraints of work, child care, school, and simply forgetting, while declining adherence over time is more associated with intentional non-adherence, and it is more likely that these patients are not aware of the consequences of stopping early. Despite being unintentional, patients who systematically forgot to take a pill every day were more aware of being non-adherent than those who had a priori intentional non-adherence, since nearly 80% of the former respondents admitted having forgotten to take some doses vs. 60% of the latter who did so. Patients who stopped taking antibiotics as they started to get better, those who limited their use because of some misbeliefs, and those who planned to have an antibiotic supply at home are supposed to have excellent adherence at the beginning of treatment and a deteriorating adherence after some days, but curiously only 10% of these patients stopped the treatment too soon. The remaining 90% of these patients actually decreased the frequency of the doses after a period of perfect adherence. This probably means that most of the patients with declining adherence over time were aware that taking the antibiotics was necessary and felt guilty about stopping to take them.

The number of adherence types is likely to vary with the study population under analysis. In studies involving long-term conditions, other typologies of medication use behavior have been detected, such as improving adherence over time. For example, Knafl et al.¹³ identified 10 adherence types for subjects with HIV on antiretroviral medications, including seven relatively consistent, one deteriorating, and two improving adherence types. However, with treatment lengths of up to 10 days, such as the schedule addressed in our study, the number of medication use behaviors is much lower, with three typologies being the most common – one of good adherence and two basic patterns of non-adherence. We only included outpatients with relatively benign acute conditions

and this fact might explain why so many patients failed to present excellent adherence behavior.

Another conclusion of this study is that medication adherence measured by the self-reported adherence question was remarkably higher than that objectively measured by MEMS, indicating that self-reporting seems to be prone to overestimating of true adherence. To our knowledge this is the first time that a self-reported question has been used to report the adherence of patients in acute infectious diseases. The main explanation that may underlie the difference between self-reported and 'true' adherence is that patients may not want to admit that they are non-adherent, and therefore reported adherence. Self-reported adherence is able to detect non-adherence when the patient reports forgetting some doses, since a patient who admits not having forgotten any dose can be either adherent or non-adherent with respect to timing and dosing. Therefore this screening question has little value in clinical practice.

There were some limitations to this study. The adherence data analyzed were collected electronically using MEMS caps. Cap openings do not always necessarily correspond to actual medication-taking. Patients may sometimes have removed multiple doses at one cap opening in order to put them in pill boxes, in which case the cap openings underestimate actual adherence. Moreover, multiple openings of the container within a period of less than 15 min were not counted. Neither can we ensure that when phenoxymethylpenicillin and the new pharmacokinetically enhanced formulation of amoxicillin/clavulanate were administered, the patients took two tablets at the same time. The diagnosis was clinical and therefore it cannot be guaranteed that all the episodes included were actually bacterial infections; however this could have happened equally in all the treatment regimens and should not be directly related to the adherence to treatment. Nonetheless, we believe that the electronic method used in this study, the large sample studied, and the fact that the patients were not informed as to the real objective of the study until the second visit, undoubtedly constitute the greatest strengths of this study.

In conclusion, less than half of the patients treated with regular courses of antibiotics presented excellent or acceptable adherence. Approximately one in four patients presented non-adherence to correct dosing and approximately one in four presented declining adherence over time. The adherence outcomes were consistently and significantly worse with three times-daily antibiotic schedules

and better with once-daily antibiotic regimens. The self-reported adherence question presented a significant negative predictive value but its low positive predictive value makes this method inappropriate for use in clinical practice.

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